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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,503	02/07/2002	Benoit Salomon	3665-21	7318

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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,503	SALOMON ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *5,15,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The **examiner** of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Michail Belyavskyi, Group Art Unit 1644, Technology Center 1600

Claims 1-18 are pending

2. Applicant's election with traverse of Group I, claims 1-14 and 16 in Response to Restriction Requirement, filed on 10/14/03 is acknowledged. Applicant traverse the Restriction Requirement on the grounds that the search of Groups I-II together would not constitute a serious search burden on the examiner and that search of the claims of Group I would provide useful information for the claims of Group II .

This is not found persuasive because the MPEP 803 (August 2001) states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The Restriction Requirement enunciated in the previous Office Action meets this criteria and therefore establishes that serious burden is placed on the examiner by the examination of more than one Group. The Inventions are distinct for reasons elaborated in the previous Office Action and above.

The requirement is still deemed proper and is therefore made FINAL.

3. Upon further consideration, it has been noticed that in the previous Office Action claim 5 was mistakenly grouped with the elected Group I. The invention of the elected Group I, (now claims 1-4, 6-14 and 16) drawn to a method of treating an immune disease using non-genetically altered T cells. The invention of claim 5 drawn to a method of treating an immune disease using genetically modified T cells. These inventions are different methods because they are different with respect to ingredients, method steps, and endpoints; therefore, each method is patentably distinct. The examiner apologizes for a mistake in the previous Office Action.

Claims 5, 15, 17-18 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-4, 6-14 and 16 drawn to a method of treating an immune disease using non-genetically altered immunoregulatory T cells under consideration in the instant application.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 6-14 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment of graft versus host disease (GVHD), comprising administering to a subject an effective amount of CD4+CD25+ cells does not reasonably provide **enablement** for a method of treatment of *any* immune disease in a subject, comprising administering to a subject an effective amount of *any* immunoregulatory T cells, as recited in claims 1-4, 6, 8-10, 13,14,16; or a method of treatment of an immune disease in a subject, comprising administering to a subject an effective amount of *any* immunoregulatory T cells, whrein the treatment is preventing or curative, as recited in claims 11 and 12. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification only discloses: (i) a murine model data of delayed GVHD in B6xD2 mice when said mice were grafted with BM transplant supplemented with $5x10^6$ CD4+CD25+ purified T cell (Example 1- 3 of the Specification as filed); (ii) ex vivo expantion of said subpopulation of T cells in the presence of IL-2 while retaining their ability to delayed GVHD in B6xD2 mice (see example 4 of the Specification as filed). The specification does not adequately teach how to effectively treat any immune disease by administering an effective amount of any immunoregulatory T cells. Moreover, no animals were used as model system to effectively treat any immune disease , comprising administering to the subject an effective amount of any immunoregulatory T cells. Since there is no animal model studies and data in the specification to show the effectively of treatment of an immune disease after administering to the subject an effective amount of any immunoregulatory T cells. it is unpredictable how to correlate limited *in vivo* data with claimed use. Feldman et al (Transplant. Proc. 1998, 30, 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading

to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Taylor et al (Blood, 2002, V.99, pages 3493-3488) teaches that immune regulatory cells are very heterogeneous population. Therefore different method of activation and expantion may result in distinct population of cells with potentially different suppressor/effector function. Various protocols would be required for different cells to be used for immunotherapy. Moreover, Applicant himself acknowledge that the ability freshly isolated CD4+CD25+ T cells to delay GVHD was unexpected (page 14, line 11 of the Specification as filed) . As such, the invention must be considered unpredictable.

In addition, the method of treating any immune disease, by administering to subject therapeutically effective amount of any immunoregulatory T cells can be species- and model-dependent (see Van Noort et al. International Review of Cytology, 1998, v.178, pages 127-204, Table III in particular) , it is not clear that reliance on the limited *in vivo* studies accurately reflects the relative mammal and human efficacy of the claimed therapeutic strategy. The specification does not teach how to extrapolate data obtained from a murine model data of delayed GVHD in B6xD2 mice when said mice were grafted with BM transplant supplemented with $5x10^6$ CD4+CD25+ purified T cell to the development of effective *in vivo* mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of treating any immune disease, by administering to subject therapeutically effective amount of any immunoregulatory T cells.

The specification does not provide sufficient teaching as to how it can be assessed that treatment of any immune disease including autoimmune disease, allergy, organ transplant rejection and viro-induced immunopathology was achieved after the administration of a therapeutically effective amount of any immunoregulatory T cells. Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of treatment of any immune disease including autoimmune disease, allergy, organ transplant rejection and viro-induced immunopathology , comprising administering an effective amount of any immunoregulatory T cells in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Also the issue that , the burden of enabling the prevention or curative of a disease (ie. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition. Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to any immune disease (for example autoimmune disease, allergy, organ transplant rejection and viro-induced immunopathology including HIV infection and AIDS) within the scope of the presently claimed invention. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compounds

in preventing these disease states. Additionally, the specification fails to enable "treatment" to the extent such treatment includes the prevention of a disease state . Accordingly, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. Claims 1-4, 6-14 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a method of treatment of graft versus host disease (GVHD), comprising administering to a subject an effective amount of CD4+CD25+ cells .

Applicant is not in possession of : a method of treatment of *any* immune disease in a subject, including autoimmune disease, allergy, organ transplant rejection and viro-induced immunopathology comprising administering to a subject an effective amount of *any* immunoregulatory T cells, or a method of treatment of any immune disease in a subject, including autoimmune disease, allergy, organ transplant rejection and viro-induced immunopathology comprising administering to a subject an effective amount of *any* immunoregulatory T cells, whrein the treatment is preventing or curative.

Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all immunoregulatory T cells recited in the instant claims. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. . See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons

of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published of a national application published under section 122(b) only if the international application designation the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

8. Claims 1-3, 7-10, are rejected under 35 U.S.C. 102(a) as being anticipated by Taylor et al (J Exp. Med. Vo.193, pages 1311-1317).

Taylor et al teach a method of treatment of an autoimmune disease in a subject comprising administering to a subject an effective amount of freshly isolated CD4+CD25+ T cells(see entire document, Abstract and page 1312 in particular). Taylor et al teach that said CD4+CD25+ T cells are obtained by a method comprising providing a biological sample comprising lymphocytes , isolating CD4+CD25+ T cells, and conditioning said cells (see Material and Method, in particular). Taylor et al teach that said T cells are allogeneic with respect to the subject to be treated.

The reference teaching anticipates the claimed invention.

9. Claims 1-4, 7-10, 13, 14 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 2002072799 or by US Patent NO: 2002/0090724 or by US Patent NO: 2003/0157057

WO' 799 teaches a method of treatment immune disease, including GVHD in a subject undergoing allogeneic organ transplantation and autoimmune disease , comprising administering to a subject an effective amount of freshly isolated CD4+CD25+ T cells(see entire document, Abstract and columns 2, lines 25-30 and 6, line 5-20 in particular). WO' 799 teaches said CD4+CD25+ T cells are autologous or allogenic with respect to the subject to be treated (see column 6, lines 45-50 and column 15, lines 25-30 in particular). WO' 799 teaches CD4+CD25+

T cells can be ex vivo expanded without losing their biological function (see column 5, lines 40-45 and column8, lines 54-60 in particular). WO' 799 teaches that said CD4+CD25+ T cells are obtained by a method comprising providing a biological sample comprising lymphocytes , isolating CD4+CD25+ T cells, expanding said cells by activation in the presence of a stimulating agent and a cytokine and conditioning said cells (see overlapping columns 10-11, in particular).

US Patent '724 teaches a method of treatment immune disease, including GVHD in a subject undergoing allogeneic organ transplantation and autoimmune disease , comprising administering to a subject an effective amount of freshly isolated CD4+CD25+ T cells(see entire document, Abstract and columns 3 and 19 in particular). US Patent '724 teaches CD4+CD25+ T cells can be ex vivo expanded without losing their biological function (see columns 5 and 19 in particular). US Patent '724 teaches said CD4+CD25+ T cells are autologous or allogenic with respect to the subject to be treated (see example III in particular). US Patent '724 teaches that said CD4+CD25+ T cells are obtained by a method comprising providing a biological sample comprising lymphocytes , isolating CD4+CD25+ T cells, expanding said cells by activation in the presence of a stimulating agent and a cytokine and conditioning said cells (see example III in particular). US Patent '724 teaches that said cells are administered to a subject at the amount of about $2x10^5$ cells (see column 10 in particular).

US Patent '057 teaches a method of treatment immune disease, including GVHD in a subject undergoing allogeneic bone marrow transplantation , comprising administering to a subject an effective amount of freshly isolated CD4+CD25+ T cells together with bone marrow transplantation(see entire document, Abstract and columns 4 and 8 in particular). US Patent '057 teaches that said cells can be ex vivo expanded without losing their biological function (see columns 1 and 3 in particular). US Patent '057 teaches that said CD4+CD25+ T cells are obtained by a method comprising providing a biological sample comprising lymphocytes , isolating CD4+CD25+ T cells, expanding said cells by activation in the presence of a stimulating agent and a cytokine and conditioning said cells (see overlapping columns 4-5 in particular).

The reference teachings anticipates the claimed invention.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2002072799 or by US Patent NO: 2002/0090724 or by US Patent NO: 2003/0157057

The teachings of WO 2002072799 , US Patent NO: 2002/0090724 and US Patent NO: 2003/0157057 have been discussed, supra.

WO 2002072799 , US Patent NO: 2002/0090724 and US Patent NO: 2003/0157057 does not explicitly teach a method of treatment of an immune disease in a subject comprising administering of immunoregulatory T cells between 10^5 to 10^{10} cells.

It is clear that both the prior art and claimed method administer the same treatment to achieve the same results. It would be conventional and within the skill of the art to identify the exact dosage of immnoregulatory T cells to be administered to a subject in need. Moreover, the claimed dosage of between 10^5 to 10^{10} immunoregulatory T cells overlaps with the referenced dosage taught by US Patent '724 and is therefore an obvious variation of the reference teaching absent a showing of unobvious property. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

12. No claim is allowed.

13. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
January 7, 2003

Christina Chan

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